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THE AMERICAN
JOURNAL OF PHARMACY

MARCH, 1917

THE AIMS AND DEVELOPMENTS OF PHYTOCHEMICAL RESEARCH.[1]

By Frederick B. Power.

It is not very long ago since there was a widely prevalent conception, which apparently to some extent still exists, that the chemical examination of plants is a comparatively simple procedure, requiring for its accomplishment neither very broad chemical knowledge nor a high degree of manipulative skill. This view is doubtless to be attributed to the fact that in past years many so-called proximate analyses of plants have been conducted which consisted of but little more than the extraction of a small amount of some vegetable material with various solvents, and subjecting the products to a superficial examination. In this way it has been possible for those possessing but little chemical training to record the occurrence of such widely distributed classes of organic compounds as volatile and fatty oils, resins, sugar, tannin, and the simpler organic acids, while the larger proportion of undetermined material was, as a rule, quite conveniently designated as extractive matter. To such observations may have been added an occasional indication of the presence of an alkaloid or a glucoside.

It is not by any means my intention to deprecate or discourage such simple determinations as those to which I have alluded, provided they be accurately and intelligently conducted, for in the investigation of any vegetable material certain preliminary tests are desirable and important, both in order to obtain some general information respecting its character and for the purpose of ascertain-

[1] An address delivered before the Washington Chemical Society, November 23, 1916, and approved for publication by the Secretary of Agriculture.

ing the presence or absence of a particular compound. On the other hand, it is evident that the chemical examination of a plant should not be restricted to such narrow limits. A very much more extended and detailed study is in fact required if any contribution of value is to be made to the more exact knowledge of the constituents of plants or drugs, for no field of research can be considered to demand a more intimate acquaintance with the properties and behavior of organic compounds, or, in general, to afford a wider scope for the application of chemical knowledge and skill, than that of phytochemistry.

In contrast to the qualifications I have indicated, it will be found that much of the earlier literature pertaining to the chemical examination of plants is extremely superficial in character, and it is thus apparent that such investigations have frequently been attempted by those who were quite inadequately prepared for the task. The results obtained under such conditions are naturally of limited value, and are sometimes quite misleading. It is probably for this reason that the subject of phytochemistry appears hitherto not to have received its full measure of recognition, although it must also be considered that the application of newly developed methods and the general extension of scientific knowledge have been important factors in the achievement of such results as have attended the more recent endeavors in this field of investigation.

The subject of phytochemistry in its broadest sense may evidently be considered to comprise the application of chemical science to all conditions affecting the cultivation and growth of plants, as well as a knowledge of their constituents. It would thus be concerned, among other things, with the character and composition of the soil, the selection of suitable fertilizing material, the study of such questions as the influence of radioactive ores and residues on plant life, and also the conditions under which the economically important constituents of the plant are produced in the largest amount. As an example of the latter purpose, with which botanical knowledge and skill must naturally be associated, it may suffice to mention the efforts to increase the yield of a particular alkaloid, such as quinine from cinchona barks, or to promote the development of such other important compounds of diverse character as are afforded by various plants. In this connection it may be noted that one of the largest and most attractive fields of chemical investigation still remains practically unexplored, for comparatively little is as yet known respecting the constituents of the plants which inhabit North America, or even

those of our immediate surroundings. There can be no doubt that a careful and complete examination of this material would reveal not only much of scientific interest, but also a considerable number of substances which would be found to possess medicinal value.

The numerous applications of phytochemistry, to some of which I have briefly alluded, render it evident that it represents an important part of agricultural science. In surveying this large domain it has been deemed desirable to devote the time this evening to a consideration of the chemical characters of some plant constituents, and for the elucidation of this phase of the subject a brief account may be given of some results obtained in the course of investigations with which I have been personally associated.

Among the drugs which possess not only chemical interest, but very considerable medicinal importance, may be mentioned the so-called chaulmoogra seeds, or the fatty oil obtained therefrom.

Chaulmoogra Oil was for a long time considered to be obtained from the seeds of *Gynocardia odorata* R. Br., but chiefly through the researches of Sir David Prain, Director of the Royal Botanic Gardens at Kew, it was definitely ascertained that the seeds yielding this oil are those of the plant *Taraktogenos Kurzii* King, or, as designated by some botanists, *Hydnocarpus Kurzii* Warburg, which is a native of Burmah.

The chief use of chaulmoogra oil is in the treatment of leprosy and other skin diseases, for which it is employed both internally and externally. It is the remedy most relied upon for leprosy, and by some is regarded as a specific for that disease.

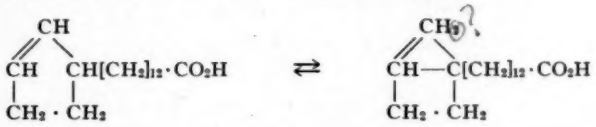
Chaulmoogra oil was first chemically examined many years ago, when, after hydrolysis, a product was obtained therefrom which received the designation of gynocardic acid, but which is now known to have consisted of an indefinite mixture. On the other hand, the more recent and complete examination of the oil has shown it to possess very exceptional chemical interest.[2] Its chief constituents are the glyceryl esters, or glycerides, of acids of an entirely new type. These acids are optically active, have a cyclic structure, and are represented by the general formula $C_nH_{2n-4}O_2$. The acid present in the oil in the largest proportion possesses the empirical formula $C_{18}H_{32}O_2$, and has been termed chaulmoogric acid, with reference to its source. For the purpose of classification in the literature, it represents, together with its homologue, the so-called chaulmoogric acid series.

[2] Power and Gornall, *Jour. Chem. Soc.*, 1904, *85*, pp. 838–851.

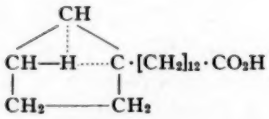
Chaulmoogric acid is a beautifully crystalline substance, melting at 68°, and having an optical rotatory power of $[\alpha]_D + 56°$. Although isomeric with linolic acid, it combines directly with only two atomic proportions of bromine or iodine, therefore has but one ethylenic linking, and must contain in its structure a closed carbon ring.

Another crystalline acid, which represents a lower homologue of chaulmoogric acid, has also been isolated from chaulmoogra oil. This acid possesses the empirical formula $C_{16}H_{28}O_2$, melts at 60°, and has $[\alpha]_D + 68°$. It has been termed hydnocarpic acid, on account of having first been obtained from a *Hydnocarpus* oil, to which reference will again be made.

A number of derivatives of both chaulmoogric and hydnocarpic acid have been prepared, and their constitution has been thoroughly elucidated.[3] They have been shown to be cyclopentene derivatives, containing an aliphatic side chain, and a consideration of their behavior towards oxidizing agents indicates them to exist in two tautomeric forms. In the case of chaulmoogric acid these two forms may be represented by the following formulæ:



The simplest expression of the constitution of chaulmoogric acid would therefore be by the following formula, in which the dotted lines represent a state of equilibrium between a hydrogen atom and two carbon atoms:



Hydnocarpic acid possesses the same structure as chaulmoogric acid, and differs from it only by containing ten methylene groups in the side chain instead of twelve.

In addition to the two acids already mentioned, chaulmoogra oil has been found to contain a relatively small proportion of palmitic acid or its glyceride, and a phytosterol. The seeds contain, further-

[3] Power and Gornall, *Jour. Chem. Soc.*, 1904, *85*, pp. 851–861, and Barrowcliff and Power, *ibid.*, 1907, *91*, pp. 557–578.

more, a considerable amount of a substance which yields hydrocyanic acid on hydrolysis, and is evidently a glucoside, but the attempts to isolate this compound have not as yet been successful.

In connection with the investigation of chaulmoogra oil, the oils expressed from two distinct species of *Hydnocarpus* seeds have also been chemically examined,[4] since they are used in their respective countries for similar purposes. One of these oils was obtained from the seeds of *Hydnocarpus Wightiana* Blume, which is a native of Western India, while the other was obtained from the seeds of *Hydnocarpus anthelmintica* Pierre, which is indigenous to Siam. The last-mentioned seeds are exported to China under the name of "Lukrabo." It may be sufficient to state that the oils obtained from the seeds of these two species of *Hydnocarpus* closely resemble chaulmoogra oil in their physical properties and chemical composition, containing the same crystalline, optically active acids, and therefore doubtless possess identical medicinal value.

Inasmuch as the seeds of *Gynocardia odorata* had for a long time been regarded as the source of chaulmoogra oil, it was deemed desirable to ascertain the character of the oil expressed from them.[5] For this purpose a quantity of perfectly authentic seeds was specially collected in Sylhet, Assam, since they are not an article of commerce, even in India. The oil from gynocardia seeds is a pale yellow liquid, whereas the true chaulmoogra oil at ordinary temperatures is a soft solid. Gynocardia oil has an odor resembling that of linseed oil, and is optically inactive. In its chemical composition, as well as in its physical properties, it bears no resemblance to chaulmoogra oil, since it contains none of the members of the chaulmoogric acid series. It consists chiefly of the glycerides of the ordinary fatty acids, such as linolic acid or its isomerides of the same series, palmitic acid, linolenic and *iso*linolenic acids, with a relatively small amount of oleic acid. The results of this chemical investigation thus served to confirm the previous botanical observations, and completely established the fact that the product known as chaulmoogra oil has never been obtained from the seeds of *Gynocardia odorata.*

It has already been noted that genuine chaulmoogra seeds contain a considerable proportion of a compound which yields hydrocyanic acid on hydrolysis, but that the attempts to effect its isola-

[4] Power and Barrowcliff, *Jour. Chem. Soc.*, 1905, *87*, pp. 884–896.
[5] Power and Barrowcliff, *ibid.*, 1905, *87*, pp. 896–900.

tion had not yet been successful. On the other hand, it has been possible to obtain from the seeds of *Gynocardia odorata* a beautifully crystalline, cyanogenetic glucoside, which possesses the empirical formula $C_{13}H_{19}O_9N$, and has been designated gynocardin.[6] It is accompanied in the seed by an enzyme, termed gynocardase, which readily hydrolyzes β-glucosides.

In connection with the subject under consideration it would appear of interest to refer to an incident in which the results of the investigation of chaulmoogra oil and related products proved to be of very considerable practical value. During the latter part of the year 1910 a number of cases of poisoning occurred in Germany through the use of a margarine which had been brought into commerce under the name of "Backa," and which was stated to have been prepared from a so-called "maratti fat," imported from India.[7] Legal proceedings were subsequently instituted against the manufacturer of the margarine, and the subject naturally attracted the attention of the health authorities as well as the general public. The investigations which ensued, in which chemists, botanists, and medical men participated, soon revealed the fact that the fat employed in the particular instance for the manufacture of margarine had been obtained from chaulmoogra seed or from the seed of one of the closely related species of *Hydnocarpus*. The identification of the fat was effected, not only by a comparison of its physical properties with those of the products which so short a time previously had been made the subject of extended research, but also by the isolation therefrom of the crystalline, optically active chaulmoogric acid.

Another native product of the East Indies, which is much more familiar through its use as a condiment than as a drug, is the *nutmeg*. It is probably not generally known, however, even among chemists, that the nutmeg when taken in considerable quantity possesses decided narcotic properties. Nevertheless, there have been in past years somewhat frequently recorded cases of so-called nutmeg poisoning, the symptoms of which are stupor and delirium, and alarming, if not fatal, consequences are said to have followed the free use of the drug in both Europe and America, as well as in India. On the other hand, in the quantities ordinarily used as a condiment or flavoring agent, the nutmeg may be regarded as perfectly harmless.

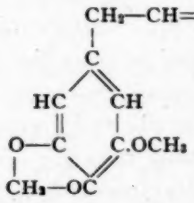
[6] Power and Lees, *Jour. Chem. Soc.*, 1905, *87*, pp. 349–357.

[7] *Zeitschr. f. Untersuchung der Nahrungs- und Genussmittel*, July, 1911, p. 226, and *Deutsche Med. Wochenschr.*, 1911, p. 53.

A desire to ascertain the nature of the toxic constituent of the nutmeg was the chief incentive to its complete chemical examination, and this yielded results of considerable interest.[8]

Although the nutmeg contains a considerable amount of a fatty oil, the more important product is the essential oil, which has been found to be of very complex composition. This essential oil contains, for example, pinene, camphene, and dipentene, eugenol and *iso*eugenol, linalool, borneol, terpineol and geraniol, safrole and myristicin, $C_{11}H_{12}O_3$. It also contains formic, acetic, butyric, and octoic acids, and an acid of the composition $C_{13}H_{18}O_3$, all in the form of esters, together with myristic acid in a free state, and some minor constituents not here enumerated. The so-called "myristicol" of earlier investigators is now known to have been a mixture of alcohols, which probably consisted chiefly of terpineol.

Physiological experiments have shown that the toxic properties of nutmeg are due to the compound known as myristicin, $C_{11}H_{12}O_3$, which is a 3-methoxy-4 : 5-methylenedioxy-1-allylbenzene:



This compound is a liquid, possessing only a faintly aromatic odor and a high boiling point, 171–173° at 40 mm. By treatment with metallic sodium or with an alcoholic solution of potassium hydroxide it is converted, through the change of the allyl into a propenyl group, into the handsomely crystalline *iso*myristicin, which melts at 44°.

The chemical interest pertaining to nutmeg is not restricted to the characterization of its constituents, or even to the determination of the physiologically active component, for the primary investigation, as is frequently the case, suggested another line of research which led to results of considerable importance. It was conceived, for example, by my associate in these investigations[9] that myristicin,

[8] Power and Salway, *Jour. Chem. Soc.*, 1907, *91*, pp. 2037–2058, and 1908, *93*, pp. 1653–1659. Also *Amer. Jour. Pharm.*, 1908, *80*, pp. 563–580.

[9] Salway, *Jour. Chem. Soc.*, 1910, *97*, pp. 1208–1219.

$C_{11}H_{12}O_3$, might serve as a starting point for the synthesis of cotarnine. As is well known, the base cotarnine, $C_{12}H_{15}O_4N$, is an oxidation product of the opium alkaloid narcotine, $C_{22}H_{23}O_7N$, and under the name of "stypticine" it is used to some extent medicinally. By an extended series of complex reactions it was indeed found possible to pass from myristicin to cotarnine, or, in other words, from a constituent of nutmeg to a derivative of an opium alkaloid. Inasmuch as cotarnine may be combined with meconine, $C_{10}H_{10}O_4$, to form narcotine, and meconine has in turn been synthesized from guaiacol, $C_6H_4\begin{matrix}OCH_3\\OH\end{matrix}$, the complete synthesis of narcotine has been effected.

It has not been the intention to devote the time this evening exclusively to such vegetable products as are obtained from the Far East, but brief consideration may be given to another Indian plant, on account of both its chemical and physiological interest. The plant in question is known botanically as *Gymnema sylvestre* R. Br., which belongs to the family of *Asclepiadaceæ,* and is indigenous to Banda and the Deccan Peninsula. Although various medicinal properties have been attributed to it by the Hindus, it was brought more prominently to notice some years ago on account of the observation that the leaves, when chewed, have the property of rendering imperceptible the sweet taste of sugar and other saccharine substances, and also, but in a less marked degree, the taste of many bitter substances. This effect is due to a substance which appears to have a selective action upon the nerve fibers or nerve endings concerned with taste, and has been designated gymnemic acid. The most recent investigation[10] of this product has shown, however, that as originally prepared it was not homogeneous,[11] and even after extended treatment for the purpose of purification it could not be obtained crystalline, nor in a form which would permit of its more definite characterization.

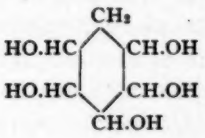
Apart from the constituent of gymnema leaves to which the peculiar physiological property referred to is due, they have been found to contain another substance of chemical interest, namely, a lævorotatory modification of quercitol, $C_6H_7(OH)_5.H_2O$.[12] The

[10] Power and Tutin, *Pharm. Journ.*, 1904, *73*, pp. 234–239.

[11] Hooper, *Pharm. Journ.*, 1887, *17*, p. 867, and *Chemical News*, 1889, *59*, p. 159.

[12] Power and Tutin, *Jour. Chem. Soc.*, 1904, *85*, pp. 624–629.

pentahydric alcohol, quercitol, which is a pentahydroxyhexahydro-



benzene, had hitherto only been known in the dextrorotatory form, as obtained from the fruits of various species of *Quercus* and some other sources. This has a specific rotation of $[\alpha]_D' + 24.16°$, whereas the new lævorotatory modification has $[\alpha]_D - 73.9°$, and the one cannot therefore be the optical antipode of the other. Inasmuch as quercitol possesses four asymmetrical groupings, a number of stereochemical modifications are possible, and the configuration of the respective dextro and lævo compounds can only be determined when the other isomerides are known.

In any consideration of the subject of phytochemistry it seems eminently desirable that some attention should be given to the plants which are indigenous to the North American Continent, for it may certainly be assumed that they are not lacking in chemical interest. The fact may, however, again be noted that comparatively few of the native plants have as yet been subjected to a complete examination, while the constituents of a large proportion of them are as yet completely unknown. A great wealth of material therefore awaits the investigator in this field of research.

Among the American plants which have been made the subjects of more recent study a few may specially be mentioned which are natives of the Pacific coast, such as *Grindelia camporum* Greene;[13] *Eriodictyon californicum* Greene,[14] or "Yerba Santa"; *Micromeria chamissonis* Greene,[15] or "Yerba Buena," and the so-called California laurel or mountain laurel, which is known botanically as *Umbellularia californica* Nutt.[16] The last-mentioned plant is of particular interest on account of the character of the essential oil contained in its leaves. This essential oil possesses an odor which at first is agreeably aromatic and somewhat camphoraceous, but when strongly

[13] Power and Tutin, *Proc. Amer. Pharm. Assoc.*, *53*, pp. 192–200, and 1907, *55*, pp. 337–344.

[14] Power and Tutin, *ibid.*, 1906, *54*, pp. 352–369, and *Jour. Chem. Soc.*, 1907, *91*, pp. 887–896.

[15] Power and Salway, *Jour. Amer. Chem. Soc.*, 1908, *30*, pp. 251–265.

[16] Power and Lees, *ibid.*, 1904, *85*, pp. 629–646.

inhaled it is exceedingly pungent, affecting particularly the mucous membranes of the nose and eyes. A complete examination of the oil has shown it to contain pinene, eugenol, eugenol methyl ether, safrole, and a considerable proportion of cineol, but its chief constituent, and that to which its peculiar pungency is due, is a ketone of the composition $C_{10}H_{14}O$, which has been designated umbellulone.

As an illustration of the chemical interest pertaining to a plant which is quite cosmopolitan in its distribution, the constituents of the common Dandelion, *Taraxacum officinale* Weber, may be briefly considered. The root of this plant, as is well known, is used to a considerable extent medicinally, and, together with extracts prepared therefrom, has long been recognized by most of the national pharmacopœias. A comparatively recent examination of English taraxacum root[17] revealed the presence of a somewhat unexpected number of interesting compounds, some of which had not heretofore been described. It was found to contain, for example, two new, handsomely crystalline, monohydric alcohols, one of which possesses the formula $C_{29}H_{47}.OH$, and has been termed taraxasterol, while the other has the formula $C_{25}H_{39}.OH$, and, being a homologue of the former compound, has been designated homotaraxasterol. Both of these compounds are members of a series, which may be represented by the general formula $C_nH_{2n-10}O$. There was also isolated a small amount of *p*-hydroxyphenylacetic acid, $C_6H_4(OH).CH_2.CO_2H$, which had not previously been observed to occur as such in the vegetable kingdom, and 3:4-dihydroxycinnamic acid, $C_6H_3(OH)_2.CH:CH.CO_2H$, together with a number of the commonly occurring fatty acids, such as oleic, linolic, palmitic, cerotic, and melissic acids. Furthermore, there was found a phytosterol glucoside, a small amount of choline, $C_5H_{15}O_2N$, and a considerable quantity of a sugar, which appeared to consist chiefly of lævulose. When an extract of taraxacum undergoes the so-called mucous or viscous fermentation, it has been observed to contain mannitol, but this does not preëxist in the root. Its formation would appear to be easily explained by the fact that the root of the plant, like other *Compositæ*, contains an abundance of inulin, which, on hydrolysis, is converted into lævulose, and the latter, by the special fermentative process referred to, becomes reduced to mannitol.

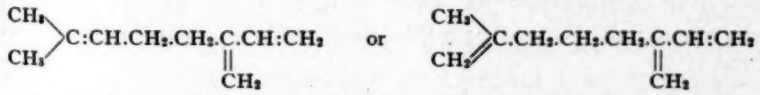
It would appear of interest to note that while the chemical examination of taraxacum was in progress it was recorded in Eng-

[17] Power and Browning, *Jour. Chem. Soc.*, 1912, *101*, pp. 2411–2429.

land that the use of an extract of this root in cases of cancer had been attended with beneficial results, and shortly afterwards attention was directed in Germany to the use of choline in the treatment of this disease. Some particular significance would seem to be imparted to these quite independent observations by the fact that taraxacum root has been found to contain choline, but the value of the suggested remedies has apparently not been further confirmed.

It occasionally happens that an investigation may gain in interest, if not in practical importance, through developments in a direction that would at first seem quite divergent from the original subject of inquiry. Some recently published researches by Russian chemists relating to the formation and chemical composition of rubber may serve to illustrate such an occurrence as I have indicated, while also helping to elucidate some problems in plant metabolism. In order, however, that the points of connection between the results of two quite distinct investigations may be more clearly apparent, the purpose and sequence of these investigations should first be explained.

A good many years ago a discussion arose respecting the solubility in alcohol of the oil of bay, as distilled from the leaves of *Myrica acris* DC., it having been stated by the Pharmacopœia that the oil was soluble in an equal weight of alcohol, whereas it was contended by some observers that it yielded a turbid solution, and consequently that the official statement was incorrect. Subsequent observations had shown that the freshly distilled oil usually yields a perfectly clear solution with 90 per cent. alcohol, but that when the oil has been kept for some time its solubility becomes impaired. In order to ascertain the cause of this change, the oil was submitted to a complete chemical examination.[18] One of the most important results was the isolation of a so-called olefinic terpene, an open chain hydrocarbon of the composition $C_{10}H_{16}$, whose constitution may probably be expressed by one of the following formulæ:



This compound, which possesses a density lower than that of the ordinary terpenes, and contains three ethylenic linkings, was the first known representative of its class, and has been designated *myrcene*. On hydration, an alcohol was produced which possessed the odor of linalool, and this on oxidation yielded citral.

[18] Power and Kleber, *Pharm. Rundschau* (New York), 1895, *13*, p. 60.

Myrcene is very susceptible to change, becoming readily polymerized by distillation under ordinary pressure or on exposure for some time to the air, with the formation of a viscid product which is very sparingly soluble in alcohol. The isolation of myrcene was not only of considerable scientific interest, but a consideration of its characters, especially its tendency to polymerize, also served to explain the apparent discrepancies of statement respecting the solubility in alcohol of oil of bay.

The more recent researches in another direction, to which I have already referred, may now be briefly considered, since they would seem to impart added interest and significance to the observed occurrence in nature of an olefinic terpene. It is well known that the hydrocarbon isoprene, C_5H_8, or $CH_2:C(CH_3).CH:CH_2$, when treated with suitable reagents, becomes polymerized, with the formation of a product having the general characters of caoutchouc or rubber, and the various processes for the production of synthetic rubber have been, in fact, chiefly based upon the utilization of this hydrocarbon. It has, however, recently been asserted[19] that all the polymerides of isoprene thusfar obtained differ from natural Para caoutchouc, inasmuch as the decomposition of their diozonides with water yields acetonylacetone and succinic acid in addition to lævulinic aldehyde and lævulinic acid. No succinic acid or acetonylacetone could be detected in the products of hydrolysis of the diozonides from natural caoutchouc. The correctness of these observations is apparently confirmed by the results of some further, quite independent investigations, which, together with the deductions from them, are of particular interest. It has been found, for example, by Russian chemists[20] that when isoprene is cautiously heated at a temperature of 80 to 90° C. it yields an open chain hydrocarbon of the composition $C_{10}H_{16}$, which contains three ethylenic linkings, and resembles the myrcene obtained from oil of bay. This new hydrocarbon has been designated by its discoverers as β-myrcene, and its most probable constitution is considered by them to be:

$$CH_2:CH.C(CH_3):CH.CH_2.CH_2.C(CH_3):CH_2.$$

It is a colorless, mobile liquid, boiling at 63° C. at 20 mm. pressure,

[19] Steimmig, *Ber. d. deutsch. chem. Ges.*, 1914, *47*, pp. 350–354.

[20] Ostromyslenski and Koschelev, *Jour. Russ. Phys.-Chem. Soc.*, 1915, *47*, pp. 1928–1931.

and is soluble in all the ordinary organic solvents. When heated at 60–70° C. with metallic sodium and barium peroxide, it is converted quantitatively into normal isoprene-caoutchouc, whereas under similar conditions isoprene gives an abnormal caoutchouc. It has thus been considered by one of the investigators[21] that this polymerization of chemically pure β-myrcene may possibly represent the only synthesis of natural caoutchouc, that is, of a substance perfectly identical with natural Para caoutchouc, both in the general structure of its nucleus and also in the position of the methyl groups and double linkings of the molecule. In this connection it has been remarked that there is every reason to believe that tropical plants synthesize caoutchouc by means of β-myrcene or myrcene-like hydrocarbons or their dimerides, and not by the polymerization of isoprene The view has furthermore been expressed that, inasmuch as compounds with an atomic grouping like that of myrcene, such as geraniol, linalool, nerol, etc., are of frequent occurrence in plants, the simple dehydration of these unsaturated alcohols would lead immediately to the corresponding myrcenes.

With consideration of the observations to which I have just referred, it would appear to be of some interest to ascertain whether myrcene or an analogous hydrocarbon is contained in plants yielding rubber. If fresh material were available, experiments in this direction could very easily be conducted.

The few examples that have been given of recent phytochemical investigations, although fragmentary in character, may serve in some measure to illustrate their development and scope. It has naturally not been possible in the short space of time to give adequate consideration to the large number of important researches which in recent years have been conducted by various other workers in this field of science. Among these there may specially be noted the contributions to the knowledge of chlorophyll and the coloring matter of flowers, and also those pertaining to the compounds which impart to flowers their fragrance. On the other hand it will doubtless be conceded that no very extended account of phytochemical investigations would be necessary in order to demonstrate their utility, for an enumeration of even a few of the organic plant constituents which have long been known and largely used, either in medicine or the arts, would alone afford sufficient evidence of the lasting benefit which such investigations may confer on mankind.

[21] Ostromyslenski, *ibid.*, pp. 1941–1947.

Although dependence must still be placed upon natural sources for many invaluable medicinal agents, such as morphine, quinine, strychnine, and other familiar representatives of the group of alkaloids, in several instances the determination of the ultimate constitution of important vegetable compounds has made it possible to prepare them synthetically, thus frequently giving rise to large and prosperous branches of industry. In briefly citing a few well-known examples of such achievements, it may be mentioned that synthetic methyl salicylate, although first produced on a manufacturing scale but a comparatively few years ago, has now displaced to a large extent the natural oils of wintergreen and sweet birch, of which it forms the chief constituent, while the salicylic acid employed in the process of manufacture is also an artificial product. Vanillin and coumarin, which represent the aromatic principles of the vanilla bean and tonka bean respectively, are now rarely obtained from these natural sources, but almost entirely by synthetic methods. Artificial indigo is now produced to the extent of several million pounds per annum, and is actively competing with the natural product, but for various reasons it has not completely displaced it. On the other hand, alizarin has long since ceased to be obtained from the root of *Rubia tinctoria* L., or Dyers' madder, being now prepared from anthracene, a constituent of coal tar.

It will be evident from the brief account of recent phytochemical research that I have now been able to present that it is not restricted in its scope to the isolation of definite organic compounds and their characterization, although this may be considered of primary importance. Its higher aim would be to determine the constitution of these compounds, and, if possible, the means for their synthetic production. A wide and most attractive field of scientific investigation is thus afforded, in which the opportunities for development are practically unlimited.

In conclusion, the hope may be expressed that the newly established phytochemical laboratory of the Bureau of Chemistry may render useful service, both in promoting the knowledge of plant constituents and in extending the applications of the knowledge pertaining thereto.

PHYTOCHEMICAL LABORATORY,
BUREAU OF CHEMISTRY.

ASSAY PROCESSES OF THE U. S. P. IX.[1]

By Philip Asher, Ph.G., M.D.

About ten days ago, when requested by the chairman of your program committee to read a paper at this meeting in lieu of the appointed speaker, who found that he would not be able to have his subject ready for the occasion, I little realized what it meant to prepare a paper of this magnitude upon such short notice. Nevertheless I have prepared a few observations relating to the assay processes of the new U. S. P. Owing to the short time at my disposal, your indulgence is asked for any omissions that may occur in this paper. Before taking up the subject of the evening, a few remarks will be apropos concerning the Pure Food and Drugs Act, and also Pharmacy.

It may not be generally known that the Pure Food and Drugs Act owes its existence to the efforts of the energetic members of the American Pharmaceutical Association. In 1901 a committee of the American Pharmaceutical Association reported that the government had established a pharmaceutical laboratory in connection with the Department of Agriculture. From that time until the final passage of the bill which has placed this law among the national statutes, the A. Ph. A. has been persistent in its efforts towards this end. It can be said without fear of gainsay that no legislation has ever been enacted that has done so much good for the conservation of the public health as this law. The people of this country owe much to the American Pharmaceutical Association for its untiring efforts in their behalf. The passage of this law has given rise to the establishment of food and drug laboratories throughout the country and this has resulted in the employment of a large number of chemists.

Pharmacy is not only the mother of medicine, but chemistry owes it a debt as well. Those familiar with the early history of chemistry are well aware that many of the men who have given their best efforts to the development of the science of chemistry had their thoughts in the domain of this science awakened in the simple apothecary shop.

[1] Read before the Louisiana Branch of the American Chemical Society, December 15, 1916.

The processes outlined in this article will show the wide range of chemical knowledge that the pharmacist should possess.

In no school where chemistry is taught, except in those institutions making chemistry a specialty, is the subject of chemistry taken up so fully as it is taught in pharmacy colleges. There is hardly a branch of chemistry that has not some pharmaceutical bearing and it is not surprising then that this subject receives the consideration it does.

U. S. P. Assay Processes.

As is well known today, the U. S. Pharmacopœia and the National Formulary are the legal standards for drugs, chemicals and their preparations. The methods of assay given therein must be strictly followed in every instance: this cannot be too strongly emphasized.

In reviewing the assay processes of the new U. S. P. in a general way, one sees that quite a number of changes have taken place, some quite radical. It is almost impossible in the time allotted to the subject to touch upon all the details, so that in a large number of instances a generalization of the methods will alone be considered; but where any general method offers any special features, these will be taken up at greater length.

There have been several errors observed in the quantities given under some of the assays, so that the writer does not wish it understood that the amounts given have been verified. It had been his intention to have done so had he had sufficient time to complete this paper in the time originally allotted to him.

For example, under potassium chlorate the quantity of acidulated ferrous sulphate is insufficient. The amount of iron sulphate is only .750 Gm., whereas the quantity required for the oxidation by .1 Gm. potassium chlorate is 1.400 Gms. Again on page 221, under ammoniated mercury, it is directed to multiply the weight of mercuric sulphide found by .162. This is wrong, it should be .862.

Acidimetry and Alkalimetry.

The following acids are assayed by titrating with normal alkali: Acetic, citric, hydrobromic, hypophosphorous, sulphuric, tartaric and trichloracetic.

Boric acid is also titrated with normal alkali, but gylycerin is used with it.

With aromatic sulphuric acid the same method is followed, but it is first refluxed six hours, the object of which is to decompose the ethyl-sulphuric acid of the compound under examination into alcohol and sulphuric acid, and thereby obtain its full acid content.

In the assay of phosphoric acid and phosphates a departure from the general method is resorted to. About 1 Gm. of the acid is accurately weighed and diluted with water to make 100 mils; 10 mils of this solution are transferred to a 100 mil flask and neutralized with special KOH T.S. (one free from chlorides), phenolphthalein being used as an indicator. To the solution 50 mils *n*/10 silver nitrate are added and then zinc oxide, free from chloride, is added in small portions to neutralize the liquid. Sufficient distilled water is added to make exactly 100 mils, and the whole agitated. The mixture is filtered through a dry filter, and to 50 mils of the filtrate 2 mils of nitric acid and 2 mils iron and ammonium sulphate T.S. are added, and the excess of silver used is titrated with *n*/10 KCNS.

In the old U. S. P., lactic acid was assayed with normal KOH, in the cold. The new directions are that after the addition of the alkali, the solution be boiled 20 minutes. This is to convert the lactones, or inner anhydrides, into the lactate. The purity rubric of the old U. S. P. was 75 per cent. By the new method a strength of 85 per cent. results, including both the lactic acid and its anhydrides.

In the assay of benzoic and salicylic acids, *n*/10 barium hydroxide is substituted for the KOH, phenolphthalein being used as an indicator. The end reaction with alkali hydroxide is not sharp, owing to the carbonate it usually contains and because the titration is conducted in the cold. Barium hydroxide has been substituted to overcome this.

There are several salts of the pharmacopœia that are assayed by acidimetry or alkalimetry: by direct titration without intermediate steps. Under the acidimetric method is potassium bitartrate. Under the alkalimetric method are the following: ammonium carbonate and hydroxide; potassium hydroxide, bicarbonate and carbonate; magnesium oxide, carbonate and hydroxide; sodium borate, carbonate, hydroxide, cacodylate and glycerophosphate; zinc stearate, carbonate and oxide.

With compounds such as zinc stearate the process slightly varies. They are first boiled with an excess of *n*/10 sulphuric acid, which

breaks up the compound into the acid and the sulphate. The excess of acid used is then titrated with *n*/10 KOH.

The direct titration of borax, sodium cacodylate, sodium glycerophosphate and others of this class, by *n*/2 HCl depends upon the property of the liberated acids from these compounds being indifferent to methyl orange. The compounds are ionized in the solution, and only the bases respond to the indicator.

In the assay of chloral hydrates, the compound is first treated with an excess of normal KOH. This converts the chloral into chloroform and potassium formate, according to the following equation:

CCl_3CHO	+	KOH	=	$CHCl_3$	+	KCO_2H.
Chloral		Potassium Hydroxide		Chloroform		Potassium Formate

The excess of alkali is then titrated with normal sulphuric acid.

Several of the compounds, such as formaldehyde and paraformaldehyde, are assayed under the acidimetric method, after having been first oxidized by peroxide of hydrogen. The compound to be assayed is treated with alkali, then with hydrogen peroxide, after which the excess of alkali used is determined by titration with sulphuric acid, litmus being used as the indicator.

Only one of the compounds of the U. S. P. is assayed by distillation, solution of ammonium acetate. The assay is carried out by adding an excess of alkali to the solution. The mixture is heated and the ammonia is distilled into a known quantity of normal sulphuric acid. The excess of acid used is determined by titration with alkali.

Metallic organic salts are directed to be assayed by first carbonizing the salt. By this process, the compound is converted into its carbonate. The cooled mass is disintegrated; the crucible and mass are transferred to a beaker. Fifty mils each of water and half-normal acid are added and the beaker covered with a watch crystal and boiled for thirty minutes. The solution is filtered and the residue washed until no longer acid to litmus. The excess of acid is titrated with alkali, with methyl orange as an indicator. The following salts are assayed by this method: calcium lactate, lithium citrate, potassium acetate, citrate, potassium and sodium tartrate, Seidlitz powder, sodium acetate, benzoate, citrate, salicylate, and strontium salicylate.

With volatile organic salts, such as ammonium benzoate and salicylate, the above method would not apply. The method used for these salts is as follows: To .5 gram of the salt, dissolved in 10 mils of water, are added 5 mils of diluted sulphuric acid. The liberated organic acids are then extracted with successive portions of 25, 15 and 10 mils of chloroform. The chloroform solution is evaporated spontaneously, 25 mils of neutral alcohol are added, and the solution titrated with *n*/10 barium hydroxide.

Gravimetric Methods.

There are quite a number of purely gravimetric methods in the U. S. P. processes. They may be divided into four classes: First, decomposition directly by heat into definite compounds, admitting of weighing and determination; secondly, precipitation; thirdly, precipitation and further decomposition of the precipitate by heat; fourthly, miscellaneous.

The following substances are assayed by the first method: calcium glycerophosphate and all the official bismuth compounds, consisting of bismuth and ammonium citrate, betanaphtholate, hydroxide, subcarbonate, subgallate, subsalicylate, and the subnitrate.

The inorganic bismuth compounds are simply incinerated; but in the case of the organic bismuth compounds nitric acid is added to completely destroy any remaining carbon, the solution evaporated to dryness and ignited, and calculated as Bi_2O_3. Under bismuth betanaphtholate, a method is also given to determine the amount of of betanaphthol present, as follows: To the salt, 10 mils of HCl are added, and the betanaphthol is extracted by successive portions of chloroform. The chloroform solution is evaporated. The residue should not weigh less than 15 per cent. of the salt taken.

Calcium glycerophosphate is assayed by dissolving in water, adding acetic acid, and then ammonium oxalate. The calcium oxalate is washed, dried and ignited, and from the weight of calcium oxide found, the glycerophosphate is calculated.

The second gravimetric method of assay, precipitation, is used for the following: ammoniated mercury and bichloride. For example, .5 Gm. of mercuric chloride is dissolved in water and acidulated with HCl, and completely precipitated by H_2S. The precipitate is filtered upon counterpoised filters and washed, first with water, then with three portions of 10 mils of alcohol. The funnel is closed with a stopper, and to remove any adhering sulphur suffi-

cient carbon tetrachloride is added to cover the precipitate. After an hour the precipitate is drained and further washed with carbon tetrachloride until the filtrate upon evaporation no longer shows any visible residue. It is further washed with alcohol, dried and weighed. The mercuric sulphide found multiplied by 1.167 gives the mercuric chloride.

The third method of gravimetric assay, precipitation and further decomposition of the precipitate by heat, is used in the following: alum, gold and sodium chloride, zinc acetate, sulphate, phenolsulphonate and valerate.

Alum is determined by precipitation as hydroxide, igniting, and weighing as oxide.

Gold and sodium chloride is assayed by the addition of KOH in excess. The potassium meta-aurate, $KAuO_2$, formed is reduced to metallic gold by the addition of peroxide of hydrogen. The precipitate is filtered, washed and ignited.

The zinc compounds are dissolved in water made slightly alkaline with ammonia water, and then precipitated as sulphide by the addition of ammonium sulphide. The precipitate, after washing, is dissolved in nitric acid, the solution evaporated, the residue ignited, and weighed as oxide.

Miscellaneous gravimetric methods of assay are used for sulphur, magnesium citrate and sulphate, and uranium nitrate.

To assay sulphur, 1 Gm. of sulphur is added to 50 mils of 10 per cent. NaOH. The resultant solution of sodium sulphide is boiled, cooled and made up to 250 mils with water. 25 mils of the above solution is oxidized by the addition of hydrogen peroxide, and heated. HCl and $BaCl_2$ are then added, and from the precipitated $BaSO_4$, after washing and igniting, the amount of sulphur is calculated. With this method a blank is run, using the same quantity of solution, but omitting the sulphur.

The solution of magnesium citrate is first evaporated to dryness, then carbonized, and the carbonized mass treated with HCl. To the well-washed filtrate, sodium phosphate is added and ammonium water, and the precipitated magnesium ammonium phosphate, after washing and drying, is ignited, and from the magnesium pyrophosphate obtained the citrate is determined. Magnesium sulphate is also determined in a similar manner. In this case carbonization is unnecessary.

Uranium nitrate. The salt is dissolved in water, and to the

heated solution ammonia water is added until precipitation is complete. After washing with ammonium nitrate solution, it is dried and gently ignited, and weighed as urano-uranic oxide, U_3O_8.

Volatile Oils.

The methods of ascertaining the purities of the volatile oils of the U. S. P., other than methods for determining their physical constants, such as polariscopic, refractometric and gravity methods, may be divided into several groups: Saponification, for the determination of esters and phenols; acetylization, for determining the alcohols; treatment with phenylhydrazine, for aldehydes; and solution in sodium sulphite.

With oil of peppermint, two distinct assays are carried out. First, for the amount of ester, and secondly, for the menthol. The ester of oil of peppermint is menthyl acetate, $C_{10}H_{19}C_2H_3O_2$, of which not less than five per cent. should be present. The assay is carried out as follows: 10 mils of the oil, the exact weight of which has been found, are treated with 25 mils of half-normal alcoholic KOH, and refluxed for one hour. After cooling, the excess of alkali is titrated with *n/2* sulphuric acid, and the number of mils of alkali used multiplied by 9.909, and divided by the weight of oil taken, gives the percentage of ester. For menthol: The official requirements are that it should contain 50 per cent. total menthol free and as ester. 10 mils of the oil are introduced into an acetylization flask, to which are added 10 mils of acetic anhydride and about 1 Gm. anhydrous sodium acetate. This is heated for one hour, allowed to cool, and the acetylized oil washed with water and solution sodium carbonate, until the washing is slightly alkaline to phenolphthalein. The oil is then dried by adding calcium chloride, filtered, and 5 mils of it, after weighing, are placed in a flask, 50 mils of half-normal alkali added, and refluxed one hour. After cooling, the residual alkali is titrated with half-normal sulphuric acid, and from the following formula the percentage of menthol is calculated.

$$\text{Percentage of menthol} = \frac{A \times 7.808}{B - (A \times .021)}.$$

A represents the number of mils half-normal alkali used in the saponification. 7.808 is 100 times the amount of menthol corresponding to each mil of half-normal KOH, the molecular weight

of menthol being 156.16. *B* represents the weight of acetylized oil used. But as the calculation must be made upon the basis of menthol, the difference between the molecular weights of menthyl acetate and menthol must be subtracted from it for each mil of KOH consumed.

Menthyl acetate is $C_{10}H_{19}C_2H_3O_2$	M. W. 198.18
Menthol is $C_{10}H_{19}OH$	M. W. 156.16
The difference between the molecular weights is	42.02

In the saponification of the ester one molecule of menthyl acetate requires one molecule of KOH. If calculated upon the basis of half-normal alkali 2,000 mils would be required. Dividing this difference of molecular weights, 42.02, by 2,000 a quotient of .021 is obtained, and this is the coefficient for each mil half-normal alkali consumed.

Oil of rosemary and sandalwood are assayed by the same method. The changes in calculation are $A \times 7.707$ for the former and $A \times 11.11$ for the latter. The ester of rosemary is bornyl acetate, $C_{10}H_{17}C_2H_3O_2$ (M. W. 196.16), of which not less than 2 per cent. must be present. The alcohol is borneol, $C_{10}H_{17}OH$ (M. W. 154.14), of which the oil should contain not less than 10 per cent. of total borneol.

Oil of sandalwood should contain not less than 90 per cent. of the alcohols calculated as santalol, $C_{15}H_{25}OH$ (M. W. 222.2).

Two of the volatile oils, caraway and cinnamon, are assayed by the sulphite method, depending upon the property that one of the principles is soluble in sodium sulphite solution and the other insoluble. *Oil of caraway.* 10 mils of the oil are placed in a cassia flask, and 50 mils of neutral saturated sodium sulphite solution are added. The mixture is heated on a water bath, and the flask is repeatedly shaken, and the mixture neutralized by additions of dilute acetic acid. When cool, sufficient solution of sodium sulphite is added to raise the lower limit of the oil within the graduated portion of the flask. The decrease in volume subtracted from the volume originally taken will give the value of carvone, $C_{10}H_{14}O$, present, which, when divided by the volume originally taken, gives per cent. by volume of carvone. Carvone is a ketone, isomeric with carvacrol and thymol. Carvacrol and thymol are phenols. In the former, the (OH) is in the ortho position, and in the latter, it is in the meta postion.

The same method is followed in the assay of oil of cinnamon as with caraway. The requirements are that it should contain not less than eighty per cent. by volume of cinnamic aldehyde, C_9H_8O. In this instance, cinnamic aldehyde forms with the acid sodium sulphite an additive compound, formerly called sodium bisulphite cinnamic aldehyde or, as it is now called, sodium cinnamalhydroxysulphonate. $C_6H_5 \cdot CH : CH \cdot CHO + NaHSO_3 = C_6H_5CH : CH \cdot CHO \cdot NaHSO_3$. Under the influence of water, the additive compound splits up into cinnamic aldehyde and sodium sulphocinnamalhydroxysulphonate.

$$2C_8H_7COHNaHSO_3 = C_8H_7CHO + C_6H_5CH_2CH(SO_3Na)COHNaHSO_3.$$

Sodium Cinnamalhydroxysulphonate — Cinnamic Aldehyde — Sodium Sulphocinnamalhydroxysulphonate

This latter compound is soluble in excess of sodium bisulphide.

With some oils, like bitter almond and lemon, the sulphite method does not give satisfactory results. In the new U. S. P. these oils are tested by the phenyl hydrazine method.

Oil of bitter almond. About 3 Gm. of freshly re-distilled phenylhydrazine is dissolved in 60 mils alcohol, and 25 mils of this solution is titrated with half-normal hydrochloric acid. To about 1 Gm. of oil accurately weighed 25 mils of the above solution is added and allowed to stand one hour, to form benzal phenylhydrozone.

$$C_6H_5NHNH_2 + C_6H_5CHO = C_6H_5CH \cdot NNHC_6H_5 + H_2O.$$

Phenylhydrazine — Benzaldehyde — Benzal Phenylhydrozone

One drop of methyl orange is added and an excess of half-normal HCl. The mixture is filtered and washed until it no longer gives an acid reaction to litmus. The excess of HCl is titrated with *n/2* KOH. Subtracting the number of mils consumed in the former from the amount used in the phenylhydrazine test, and the difference multiplied by .053 gives the benzaldehyde present. In the titration of phenylhydrazine with HCl, phenylhydrazine chloride is formed. When the aldehyde is added to phenylhydrazine, phenylhydrazone is formed.

Oil of bitter almond also contains hydrocyanic acid, and its determination is carried out as follows: To a solution of magnesium sulphate a definite amount of NaOH is added, to form magnesium

hydroxide. Two drops potassium chromate are added, and then sufficient silver nitrate to produce a red tint. To the mixture thus prepared a weighed quantity of the oil to be tested is then added and titrated with *n*/10 silver nitrate.

Oil of lemon. The aldehyde present in this oil is citral, $C_{10}H_{16}O$ (M. W. 152.13), of which it should contain not less than 4 per cent. Its method of assay is similar to that of benzaldehyde, with but slight modifications.

Eugenol, allyl guaiacol, $C_6H_3OCH_3CH_3OH$. Several of the official oils, such as cloves, allspice, etc., contain this principle. The assay is readily carried out by placing 10 mils of the oil in a cassia flask and shaking for 5 minutes, after which it is heated for 10 minutes on a water bath, cooled, the liquid allowed to separate and sufficient KOH added to raise the lower level of the oil within the graduated part of the neck, and noting the volume of residual liquid. The alkali converts the phenol into a soluble sodium compound.

Oil of thyme should contain not less than 20 per cent. by volume of phenol. Its assay is like the above.

Oil of mustard presents a method of assay different from all others. It owes its property to allyl-isothiocyanate, C_3H_5SCN, of which not less than 92 per cent. should be present. 4 mils of the oil, accurately weighed, are diluted with alcohol to make exactly 100 mils. 5 mils of this solution are placed in a 100 mil flask, and 50 mils of *n*/10 silver nitrate are added, and 5 mils of ammonia water. The flask is connected with a reflux condenser and heated for one hour. After cooling, it is made up with water to 100 mils, mixed and filtered. 50 mils of the filtrate, after treating with nitric acid and iron indicator, is titrated with KCNS. The allyl-isothiocyanate is converted by the ammonia into thiosinamine:

$$\underset{\text{Allyl-isothiocyanate}}{C_3H_5NCS} + \underset{\text{Ammonia}}{NH_3} = \underset{\text{Thiosinamine}}{C_3H_5NHNH_2CS.}$$

The action of the silver oxide produced by adding ammonia water to silver nitrate, removes the sulphur as silver sulphide, with the formation of allyl-cyanamide:

$$\underset{\text{isothiocyanite}}{C_3H_5NHNH_2CS} + \underset{\substack{\text{Silver}\\\text{Oxide}}}{Ag_2O} = \underset{\substack{\text{Sulphide}\\\text{Silver}}}{Ag_2S} + \underset{\text{Allyl-cyanamide}}{CNNHC_3H_5} + H_2O.$$

In the assay of oil of eucalyptus another foreign condition is met. This oil contains eucalyptol or cineol, $C_{10}H_{18}O$, of which not less than 70 per cent. by volume shall be present.

The assay directs that 10 mils of the oil be placed in a round-bottom glass dish, imbedded in finely broken ice. 10 mils of arsenic acid T.S. are added and stirred until precipitation is complete. When the mixture ceases to congeal further, it is allowed to stand 10 minutes in the ice bath. Upon the expiration of this time, it is transferred to a hard filter paper and covered with another paper, the whole being surrounded by filter papers and placed between the plates of a press to remove all liquids. When completely dry, the eucalyptol arsenate is transferred to a cassia flask and hot water added, and the flask placed in boiling water. This decomposes the eucalyptol arsenate into eucalyptol. When cool, sufficient water is added to raise the eucalyptol to a level where it can be read.

CHLORIDES, IODIDES AND BROMIDES.

The salts of chlorides, iodides and bromides are similarly determined. The weighed amount is placed in a 200-mil flask and dissolved in 25 mils of water. 50 mils *n*/10 silver nitrate is added, 5 mils of nitric acid, and sufficient water to make 200 mils. Mix and filter. The first 20 mils of the filtrate are rejected. 100 mils of the filtrate, after treating with nitric acid and iron and ammonium sulphate T.S., are titrated with *n*/10 KCNS.

Hydrocyanic acid and sodium cyanide are determined by the silver nitrate method, with potassium iodide as an indicator. To the HCN, KOH is added. The silver nitrate produces the double cyanide of silver and potassium, which is not affected by the alkali. Further addition of silver causes a decomposition, the insoluble silver cyanide separating; the silver cyanide then reacts with the potassium iodide, forming silver iodide, which is shown by the production of a yellow color.

The silver method is also used for the determination of the soluble phosphates and the hypophosphites. The hypophosphites are first oxidized to the phosphates by nitric acid, and the methods then followed as under phosphoric acid.

(*To be continued.*)

QUARTERLY REVIEW ON THE ADVANCES IN MATERIA MEDICA AND PHARMACY.

By John K. Thum, Ph.G., Pharmacist at the German Hospital, Philadelphia, Pa.

Solution of Magnesium Hypochlorite.—The so-called Carrel or Dakin Solution, which is nothing more or less than the well-known Labarraque solution, considerably modified as to chlorine content, reduced to one fifth available chlorine, in fact, and the alkalinity very much decreased, is regarded by some as too unstable. Some surgeons seem to think that it gives up its chlorine too readily and consequently its antiseptic action is soon spent. To obviate this it has been suggested that a magnesium hypochlorite solution, because of its greater stability, would be eminently more desirable, besides being isotonic with the blood-serum. It is likewise said to be without harm to the cells, and very much less irritating. But it is also suggested that this solution be warmed to 95° F., before using, and that is the great disadvantage. To warm the solution will require great care, and such care is not always possible where many cases are dressed within a certain time, as must be the case in the great war zone, where the demand for antiseptic solutions is urgent and frequent. The use of the Carrel-Dakin Solution is becoming quite general at the present time in this country, and if it has any disadvantages that can be avoided by using another solution, such a solution should be available. The magnesium hypochlorite solution is made as follows:

Chlorinated lime	28.0 gm.
Magnesium sulphate	18.20 gm.
Water	1000.0 mils.

Put the chlorinated lime in a well-covered container with 900 mils of water and stir frequently for 6 hours; dissolve the magnesium sulphate in 100 mils of water; mix both solutions thoroughly and filter rapidly, taking care to conduct the operation with as little exposure to air and light, as possible. Only such quantities should be made as will be used within a short time.

The Property in a Prescription.—While the following interesting case was decided in a London court, yet it will undoubtedly be worth while to bring it to the attention of American pharmacists. In

this country the question "To whom does the prescription belong?" has been a matter of debate since time immemorial. Anything that will in any manner bear on the subject and help to clear it up must be pertinent: "A woman consulted a physician who gave her a prescription which she took to a firm of pharmacists to be dispensed. The prescription was not returned to her, and when her husband asked that it should be, this was refused, the pharmacists stating that they had undertaken at the request of the physician not to return his prescriptions to patients unless they were expressly authorized by him to do so. An action was brought by the husband against the pharmacists for the return of the prescription. In giving evidence, the physician stated that the course adopted by him with regard to prescriptions was taken for the protection of the public. He illustrated the danger of allowing prescriptions to be retained by the patient by saying that not infrequently a medicine ordered for an adult was given, without any physician being consulted, to an infant. He had requested pharmacists to inform him whenever a patient asked for the return of a prescription, and he made a practice of writing on prescriptions which might properly be handed back without question the words "return to patient." The lawyer pointed out that the prescription was of no value to them, and that they were only contesting the case on the question of principle and in order to keep faith with the medical profession. The judge held that no property in the document had passed to the plaintiff, as the prescription had been handed to the patient only in order that it might be conveyed by her to the pharmacists to be made up instead of the medical man himself sending it. The claim, therefore, was dismissed with costs." (*Jour. A. M. A.*, Nov. 25, 1916.)

The Effect of Various Salts and Alkalis on Pepsin.—Hamburger and Halphen make some interesting comments in reference to their experiments with pepsin and the action of salts and alkalis on the same. Pepsin, they state, is completely inactive when treated with salts. Yet they found that sodium chloride in the strength of a 1 to 1,000 solution markedly increases the activity of this ferment, although in a concentration of 1 to 400 solution it seems to have no effect whatever, and a 1 to 40 strength solution renders the ferment completely inactive. They also found that other salts of a neutral character gave similar results. And, as was to be expected, alkalis they found were much more inhibitive. Perhaps the most interesting of their observations is that free hydrochloric acid, in the propor-

tion of 7 to 1,000 up to 9 to 1,000 seems to completely arrest peptic activity. Further work along the last statement of results obtained would be of value. (*Arch. Intern. Med.*, Chem. Abstr., 1916, 10, 2585.)

The Atomic Weight of Lead.—This determination was made from lead oxide prepared from pure lead nitrate, and the result showed that the atomic weight of the metal is 206.98. In 1904, the International Commission adopted 206.9 as the atomic weight. The experimenters also determined the weight of lead extracted from uraniferous minerals. Getting rid as far as possible of any lead which was not of radio-active origin, they found the atomic weight of radio-active lead to be 206.71, which is close to that found by Honigschmidt and Horowitz. (*Compt. rend.*, 1916, 163, 514.)

Fraudulent Drug Traffic Checked.—Fraudulent traffic in imitations of certain synthetic drugs used by physicians has been checked by the joint action of federal, state, and municipal officials, according to the report of the Chief of the Bureau of Chemistry, United States Department of Agriculture. Because of the high prices demanded for such drugs, cheap imitations, with little or none of the therapeutic properties of the genuine, have been put on the market under the names and labels of the real drugs. Shipments were seized, and a number of individuals were prosecuted successfully, under the Federal Food and Drugs Act, and indictments were procured under the postal laws, but the traffic could not be wholly suppressed under the federal laws, nor could all offenders be reached. The department of agriculture thereupon laid the matter before the state and municipal officials, with the result that many prosecutions were instituted and seizures made by them. Ultimately, through joint action, the traffic was suppressed. (*Jour. A. M. A.*, Jan. 13, 1917, p. 130.)

No Importation of "Patent Medicines" Permitted Into Germany.—According to the *Münchener Medizinische Wochenschrift* the Imperial Government has issued an order to the effect that no unnecessary articles will be permitted to be brought into the country, and among other things, this prohibition applies to proprietary medicines. This order applies until further notice. It seems like very gentle irony, indeed, when the country that manufactures more patent medicines than any other, is forced by its government to go on record that this class of products is "unnecessary!" (*Jour. A. M. A.*, Jan. 13, 1917, p. 130.)

The Administration of Deliquescent Drugs in Capsules.—Dr. N. G. Davis, of Chicago, recommends the use of a mixture of one part of beeswax and three parts of castor oil as an excipient for giving salts, such as potassium iodid, sodium or potassium bromid, etc., in capsule. He states that he has given iodine, the element itself, by mixing with every two grains, at least five grains of this wax mass. He also recommends its use for giving guaiacol, oil of sandalwood, and drugs of like similarity. We have found, however, that the wax mass in the proportions of one of beeswax and three of castor oil does not work out. But by reversing the parts it works admirably. (*Jour. A. M. A.*, 1160, 1916.)

Sulpho-Titanic Reagent to Differentiate Alpha and Beta Naphthol.—Titanic anhydride gives marked color reactions with phenolic bodies, a fact known for some time. It has now been discovered that titanic anhydride (native) heated with sulphuric acid at near the boiling point for several hours, and the clear solution decanted, as only a small quantity of the rutile is dissolved, is very useful for identifying alkaloids containing a phenolic group. The reagent is said to be permanent. Morphine gives a blood-red color; apomorphine, a reddish-violet; oxydimorphine, a wine-red; cuprein, an orange shade, something like that of alkali dichromate; hordenine, deep orange; tyrosine, a color something like that given by hordenine; adrenalin, a reddish-brown color. Alkaloids without the phenolic grouping give no reaction. It was also found that this reagent is a particularly sensitive test for the presence of hydrogen peroxide. Furthermore, it was also found that this reagent is an excellent means for differentiating between a- and b-naphthol. A very small quantity shaken in a test tube with two or three mils of this reagent gives forth an intense green color in the case of a-naphthol, and a most decided blood-red color with b-naphthol. If the substance is first dissolved in glacial acetic acid, and the sulpho-titanic reagent is added to the solution, a green ring surmounted by a reddish-violet zone distinguishes a-naphthol; while a blood-red ring indicates b-naphthol. (G. Deniges, *Annales Chim.; Analyst*, 1916, 21, 213.)

Mustard Seed as a Laxative.—Although not generally known, whole mustard seed has been used for many years as a laxative in some countries. In the course of a rather extensive investigation as to why it has this laxative action it was noticed that the odor of hydrogen sulphide had developed in a bottle containing the water in which the seed had been placed the day before. It was reasoned

that the activity of the seed as a laxative is probably due to this generation of hydrogen sulphide and likely to the carbon dioxide which is also formed at the same time, both of which are known to promote peristalsis. The statement is made that this also explains the cyanosis in cases of poisoning by this seed. When this gas is readily eliminated by the lungs there is no untoward action. (*Jour. A. M. A.*, 1916, 1404.)

The Adsorption Theory in Practical Medicine.—The power of aluminum hydroxide and aluminum silicate to adsorb albuminous substances is being made use of in medicine in a practical way in the treatment of the various grastro-intestinal disturbances. In order to be effective it is necessary to give extremely large doses. So far as is yet known no untoward results have occurred, although some observers mention the fact that these drugs show a tendency to form concretions in the bowel and therefore may be the means of more or less obstruction. This power of adsorption exhibited by these drugs resembles in a manner the action of white bole in the treatment of cholera, and likewise the adsorption of toxins from sera. In view of the work done by Lloyd in this country, in connection with hydrous aluminum silicate and its power to separate alkaloids from drugs containing them, it is just possible that many of the pathological conditions produced in the gastro-intestinal tract, for which hydrous aluminum silicate has been used with apparent good effect, may be due to alkaloidal bodies, or bodies closely resembling them. (*J. Russ. Phys. Chem.*, Chem. Abstr., 1916, 10, 2659.)

Rhodoform, a New Dental Antiseptic.—The chemical name of this drug is methylhexamethylenetetramine thiocyanate, and is said to contain 37 per cent. of thiocyanic acid. It is a brown powder, without odor, and melts at 143° C. It is said to be of value as an antiseptic in stomatology. (*Boll. Chim. Farm.*, Chem. Abstr., 1916, 10, 2498.)

Rapidity with which Alcohol and Sugars May Serve as Nutriment.—It is stated that alcohol commences to be burned within five to eleven minutes after taken on an empty stomach. Sucrose, lævulose, begins to be burned as soon, and probably sooner. Dextrose and maltose are burned not quite so rapidly, taking at least from twenty to thirty minutes for complete combustion and utilization in the processes of metabolism. It is also stated that lævulose, and very often galactose, has a tendency to change into fat in the body. And dextrose tends to change to glycogen, and is stored as such. (*Amer. J. Physiol.*, Chem. Abstr., 1916, 10, 2591.)

Influence of Methyl Salicylate on the Production of Bile.—It has been shown by experimentation on guinea pigs, that methyl salicylate, given either by mouth or hypodermatically, causes an increased secretion of bile, and simultaneously an increase in the total solids of that secretion. A number of experiments on animals on standard diet, and under treatment with this drug, while showing greater output of bile and its products, yet did not show any loss of body weight. (*Jour. A. M. A.*, 1916, p. 1403.)

Chlorosis in Plants.—The author of this interesting paper states that while the commonest form of chlorosis in plants is due to deficiency in iron, this is not the only cause. A lack of manganese, magnesium, or sulphur may bring about the same condition. It is stated that lack of iron is generally due to large amounts of chalk in the soil, which has a tendency to keep back the absorption of iron. Chlorosis induced by a lack of iron is readily cured by the application of a solution of an iron salt to the soil. When caused by a lack of magnesium the condition is not so readily corrected. Chlorosis is also caused by the exudations from diseased plant cells. (*Comptes rend. Soc. biol.*, Chem. Abstr., 1916, 2500 by P. Maze.)

Incompatibility of Sodium Bicarbonate with Bismuth Salicylate, and Magnesium and Lithium Salicylates.—The formation of carbonic acid gas when dispensing a mixture of sodium bicarbonate and bismuth salicylate has been noticed by many workers, therefore this incompatibility is no new thing. It is stated that if a neutral sodium carbonate is used there is no effervescence. The same reactions occur with magnesium and lithium salicylates, and the benzoates have a similar reaction. (*Jour. Pharm. Chim.*, 1916, 353.)

Thromboplastin Solution as a Hæmostatic.—This solution is a very fine suspension of ox-brain in physiological salt solution, preserved with 0.3 per cent. of tricresol. It is said to be of great practical value in hæmorrhage but must be applied to the site of bleeding. It is also claimed to be of great value in cases of true hæmophilia, in fact, stated to be a real specific for this most distressing condition. If this is so, a wonderful discovery has been made, and it should be promptly brought to the attention of all the physicians of the world. (*Jour. A. M. A.*, p. 1717, 1916.)

A Report of the Council on Pharmacy and Chemistry.—We cannot help but feel that the following report from the Council on Pharmacy and Chemistry of the American Medical Association will prove of interest to many pharmacists, and develop a more lively

interest on the part of doctors in learning how to avoid writing for irrational combinations of drugs:

"Glycerophosphate Comp. Ampuls, 1 Cc., Squibb" are claimed to contain, in each, sodium glycerophosphate 0.1 Gm., strychnine cacodylate 0.0005 Gm., and iron cacodylate 0.01 Gm. The Council refused recognition to "Glycerophosphate Comp. Ampuls, 1 Cc., Squibb" because the name did not indicate the potent ingredients and because the administration of a mixture of sodium glycerophosphate, strychnine cacodylate and iron cacodylate is irrational.

The preceding statement was submitted to E. R. Squibb and Sons for consideration. The firm replied:

" . . . we wish to explain that there has been a small demand for this product, no doubt created by other manufacturers. We have filled hitherto this demand as far as it came to us, using the formula regularly supplied for years by other firms.

"The name Glycerophosphate Comp. to cover a product containing sodium glycerophosphate, strychnine cacodylate and iron cacodylate, seemed to us the best that could be devised, under the circumstances. It is absolutely impossible to mention all the ingredients in the name, as it would give an unwieldy title. In passing, we might mention that the U. S. P. and N. F. cover also by the word 'Compound' the potent ingredients in many titles.

"However, the finding of the Council, that the formula here in question is irrational, must determine our action, and we have, in consequence, decided to eliminate Glycerophosphate Comp. Ampuls from our list, dropping the article altogether."

This coöperation in the work of the Council on Pharmacy and Chemistry is gratifying. In passing the Council notes that the foregoing criticism of many Pharmacopœial and National Formulary titles is justified. Many Pharmacopœial preparations have names which are not only nondescriptive but actually misleading. Such are compound powder of glycyrrhiza and compound syrup of figs, both of which owe their activity to senna, and acid camphor mixture and compound mixture of glycyrrhiza, which are essentially opium preparations. If any of these preparations possess therapeutic value their names should be descriptive, as otherwise they violate a fundamental principle in the nomenclature of medicinal substances, a principle for which the Council has contended and which is supported by both the medical and pharmaceutical professions as well as by manufacturers." (*Jour. A. M. A.*, Feb. 3, 1917.)

The Sale of Anhalonium to be Regulated.—The Senate passed a bill, on the 25th of January, to amend the Harrison Narcotic Law so as to include within its provisions anhalonium, also known as mescale or muscale buttons and as pellote. It will be remembered that this plant, of which the dried tops are used, belongs to the Cactaceæ or Cactus Family. Experimentation on animals with this drug has shown it to be a powerful narcotic poison. These narcotic properties closely resemble those of opium.

Anent Aspirin.—The expiration of the patent rights on this drug is being awaited with a great deal of interest by the medical and pharmaceutical world, and, as the following news item from one of the most prominent daily papers of the country suggests, by the laity as well. And well may the laity be interested. The propaganda carried on by the patentee in the newspapers and magazines of this country in bringing this drug to the notice of the laity can have only one effect and that a most pernicious one, namely, the encouragement to self-medication on the part of the public. The news item follows:

"There are promises of lively times in pharmaceutical circles after February 17, when the United States patent on aspirin expires. This patent is held by the Bayer Company, Inc., of New York, the American representative of a German dye and chemical firm, and notice has been served that the company claims the sole right to the name aspirin as a registered trademark even after the patent expires. Legal action is hinted at in case any other concern manufactures a product and attempts to sell it under the name of aspirin.

"The chemical name of aspirin is acetyl salicylic acid. Under the patent laws of this country the Bayer Company has held a monopoly on the product, no matter what name it might be called nor what new and improved process might be used in its manufacture. In other words, during the life of the patent, the United States Government virtually took the position that all acetyl salicylic acid, no matter by whom made, was 'aspirin' and the sole right was vested in the Bayer Company.

"It is no secret that there are numerous American firms ready to go into the aspirin business after next week. What they will call their product is not known, but there certainly is a disposition to use the name of aspirin and invite a test. One company in the Philadelphia district, which has up to this time been perfecting its phenolpthalein manufacture, is about ready to jump in on aspirin,

and it is known that certain interests closely allied to this country are in favor of using the name aspirin.

"The argument is made that aspirin is a name, and not a trademark or brand; that the product was introduced as aspirin, and not as aspirin brand of acetyl salicylic acid, and that a name belongs to the object and not to the inventor of a name. If a battle comes it is likely to be fought out largely on this point, which involves positions denied by the Bayer Company." (*The Philadelphia Public Ledger,* Saturday, Feb. 10, 1917, p. 15.)

CORRESPONDENCE.

PROF. HENRY KRAEMER, Editor,
AMERICAN JOURNAL OF PHARMACY,
Philadelphia, Pa.

Dear Professor Kraemer: The following has been unanimously adopted by the members of the Council on Pharmacy and Chemistry.

W. A. PUCKNER, *Secretary.*

The death of Martin Inventius Wilbert, a member of the Council on Pharmacy and Chemistry of the American Medical Association since its organization, removes one of its most able and loyal members. He was possessed of an intellectuality and a manhood which commanded the attention and respect of the members of both the medical and the pharmaceutical professions. He was fearless, honest and unselfish. He was uncompromising in his denunciation of the evils which beset the practice of medicine and pharmacy, but was never ungracious either with his pen or in his speech. If after due deliberation he was sure that a definite policy should be promulgated to improve the conditions of these professions, he proclaimed his view and conducted a campaign that inevitably received the support and recognition of those best informed. He gave a life of service with never a thought of reward and earned every honor which was bestowed on him. His knowledge of pharmacy was such that he could have obtained prominence in the manufacturing field and with it would have come a large measure of financial reward. But he chose to devote his thoughts and energies to the general good rather than to his own profit. His influence on medicine and pharmacy was unique. The forcefulness of his personality

was equaled only by his modesty and sincerity. His greatest work—one which will be cherished as a part of the history of the American Medical Association—was his devotion to the aims and objects of the Council on Pharmacy and Chemistry and his unselfish and indefatigable labors in its behalf.

We, the members of the Council on Pharmacy and Chemistry of the American Medical Association, mourn the loss of one of our most useful associates, and one whose life may be held up to the younger generation of pharmacists as an example of unselfishness and devotion to high ideals.

PROF. HENRY KRAEMER, Editor,
AMERICAN JOURNAL OF PHARMACY,
Philadelphia, Pa.

Dear Sir: At the request of the Board of Trustees of the German Hospital, of Philadelphia, I am enclosing a copy of the Resolutions on the death of Martin I. Wilbert, adopted by them at their meeting, December 26th, 1916.

Very truly yours,

HENRY F. PAGE,
Medical Superintendent.

MARTIN INVENTIUS WILBERT.

WHEREAS, The board of trustees of the German Hospital have learned with profound sorrow of the death of Dr. Martin I. Wilbert, which occurred on November 25, 1916, at this Hospital.

WHEREAS, The late Dr. Wilbert occupied the position of apothecary in this Institution from 1891 until 1908, and director of the x-ray and photographic department from 1899 to 1908, leaving his labors with us after eighteen years of splendid service to accept a position of wider scope in the Federal Service at Washington; establishing by his signal ability and indefatigible perseverance a unique and enviable reputation in the world of medicine and pharmacy.

Resolved, That the board of trustees of the German Hospital deplore his early death at the age of fifty-one, while still in the prime of his life and activities.

Resolved, That the board of trustees tender to the family of our deceased friend their heartfelt sympathy in the loss which they have sustained.

Resolved, That a copy of this minute be sent to the members of the late Dr. Wilbert's family and that copies of these resolutions be sent to the Journal of the American Medical Association, to the Journal of the American Pharmaceutical Association and the American Journal of Pharmacy.

G. A. SCHWARZ, *President,*

ADOLF HELLWEGE, *Secretary.*

AMERICAN PHARMACEUTICAL ASSOCIATION

Editor, American Journal of Pharmacy: The Board of Canvassers of the American Pharmaceutical Association met Monday evening, December 11th and counted the ballots cast in the annual election. The following have received a plurality of the votes and are elected:

President—Charles Holzhauer, Newark, N. J.

1st Vice President—Alfred R. L. Dohme, Baltimore, Md.

2nd Vice President—Leonard A. Seltzer, Detroit, Mich.

3rd Vice President—Theo. J. Bradley, Boston, Mass.

Members of the Council—Fred. J. Wulling, Minneapolis, Minn.; G. M. Beringer, Camden, N. J.; Thos. F. Main, New York City.

Respectfully,

(Signed) A. D. THORBURN,
FRANCIS E. BIBBINS,
FRANK H. CARTER,
EDWARD W. STUCKY.

FUNERAL SERVICES OF MARTIN I. WILBERT.

Martin Inventius Wilbert died on November 25, 1916, at the German Hospital, Philadelphia. His health had been poor for the last four years, and since childhood he had been affected with a heart lesion. On Saturday morning at 9.15 o'clock he suddenly fell back on his pillow and passed away.

The funeral services were held at the chapel of the Mary J. Drexel Home, Philadelphia. This "Home" is the Motherhouse of the Lutheran Sisters who have charge of the nursing in the German Hospital and with whom Dr. Wilbert worked for so many years while connected with the "Hospital" as chief apothecary and director of the x-ray laboratory. For this reason it seemed peculiarly

fitting that the last sad rites in connection with his passing away should be held here and among the friends who knew him so long and held him in such esteem.

Amid the many floral tributes sent by his many friends and the scientific societies that claimed him as a member, lay our friend and fellow-worker, while the pastor of the "Motherhouse," the Rev. Ernest F. Bachmann, read the simple and impressive Lutheran service for the dead, and spoke eloquently of the many fine qualities of this man. The choir of the chapel, composed of Sisters, closed the services by singing Dr. Wilbert's favorite hymn, "Abide with me."

The honorary pall-bearers were Dr. Henry F. Page, Dr. William T. Shoemaker, Dr. George G. Ross, Dr. A. D. Whiting, Prof. Henry Kraemer, and Mr. John K. Thum.

Among the many who attended the services were Mr. Howard B. French, president of the Philadelphia College of Pharmacy, Prof. J. P. Remington, Prof. S. P. Sadtler, Dr. R. A. Hatcher, of New York; Dr. C. A. Weidemann, Dr. F. A. Stewart, Mr. George M. Beringer, Mr. Edwin M. Boring, Mr. William L. Cliffe, Dr. R. P. Fischelis, Mrs. Charles H. LaWall, Prof. E. G. Eberle, Mr. Ambrose Hunsberger, and from Washington, D. C., there were present the following co-workers of Dr. Wilbert in the hygienic laboratory: Dr. A. M. Stimson, Dr. Carl Voegtlin, Dr. Murray Galt Motter, Dr. George B. Roth, Dr. Albert F. Stevenson, Dr. G. A. Menge; and from the same city Dr. S. L. Hilton. Mrs. John M. Maisch, wife of one of the great leaders of pharmacy now deceased, and a warm friend of Dr. Wilbert, was also present. Dr. Marie L. Bauer was also among the many Philadelphia friends present.

The following is an abstract of the sermon delivered by the Rev. E. F. Bachmann.

When Almighty God summoned from our midst our beloved Dr. Wilbert, a life of exceptional usefulness was brought to its close, prematurely in the opinion of many. Yet, as a recently departed servant of the Lord used to say, "All the ways of God lead to Transfiguration." Let us therefore also in this instance, humbly and with unshaken confidence in God's infinite love and wisdom, bow under His Almighty hand. We whose presence to-day is a tribute of our esteem and love to our departed friend and fellow-worker, are but a small fraction of the host of friends to whom this early close of his career is a distinct loss, both to their personal life and to his profession.

There are some among you who still recall the day when Mr. Wilbert entered upon his duties as the apothecary of the German Hospital just twenty-five years ago. Though still a very young man he combined in a rare measure a scientific mind and an altruistic soul, high idealism and practical common sense, which together with his scholarly attainments and his noble simplicity of character soon gained for him the absolute confidence of the late Mr. John D. Lankenau, the great benefactor of the German Hospital, and the founder of our Mary J. Drexel Home & Philadelphia Motherhouse of Deaconnesses. Also the staff of the Hospital soon found every reason to trust his scientific and practical judgment, and our Deaconesses found in him such a staunch friend that to this day they have considered him a member of our Motherhouse-family.

His life was an example and an inspiration to all who were privileged to work with him. Though since his boyhood he never enjoyed robust health, his indomitable will forced his body to serve him to the utmost. He never worked for a salary but always for his ideals, which he sought to make realities in accordance with his life long and oft expressed conviction that the Almighty has placed us in the world for service. His ambition, to contribute at least something to the advancement and the real good of humanity, has in a large measure been attained by him even in the judgment of other leaders in his profession.

It seems providential that he was able to complete a most important task assigned to him by the Department just before he left to seek relief at the German Hospital from the attack to which he succumbed on Saturday morning. That he ended his career at that Institution in which he had begun his professional life, was the fulfillment of a wish repeatedly expressed to his most intimate friends. Though eight years ago he had accepted a call to Washington, where a larger field of usefulness with its corresponding greater influence, offered him the much coveted opportunity to bring his ideals nearer to their realization; and though his ability and his noble character gained for him there many true friends, yet he could never forget his "first love," the German Hospital and the Deaconnesses.

His life was an inspiriation, but also his end has a peculiar message for us. It came so suddenly that it shocked especially those who had briefly called on him even within his last hour. We all were taken by surprise. He himself, however, had arranged all his affairs

practically down to every detail. He had often said: "I am ready to go at any time;" we have reason to believe that he was ready. Only a few of his intimate friends know that he gave some of his deepest thought to religion, to his relation and his responsibility to God. Here then is an example of real preparedness. If we heed the call for national preparedness against an evil day that may never come, is it reason to neglect preparedness for the inevitable, our last day, when we shall have to render our account to God? There is but one true preparedness, and that is found in Christ, who with out-stretched hands calls us to Himself with the well-known invitation "Come unto me all ye that labor and are heavy laden, and I will give you rest." In Him we find forgiveness of sin, the adoption as children of God and heirs of eternal life. He stands before us full of consolation and triumph when He says: "I am the resurrection and the life; he that believeth in me shall never die." Looking up to Him, our Lord and Saviour, let us go forward in our daily task, conscious of our responsibility to Him and of our ultimate victory in Him, consecrated in utter unselfishness to Him and to His cause which finds one of its best expressions in unselfish service to our fellowmen.

NOTES FROM THE RESEARCH AND BIOLOGICAL LABORATORIES OF E. R. SQUIBB & SONS.

The Pituitary Body in Therapeutics.

By H. S. Adams.

The investigations which in recent years have built up our present knowledge of the glands of internal secretion have yielded practical results along two important lines. Of these the first is the treatment of diseases finding their origin in an abnormal condition of the gland, involving an excess or a deficiency of secretion. A second and quite as important result has been the discovery that these glands may be the source of substances of tremendous physiological activity, which may be applied to the cure of conditions not definitely associated with a diseased condition of the gland in question. Of this second class the present use of our knowledge of the pituitary body is an eminent example.

It is true that certain diseases are definitely associated with abnormalities of the pituitary, and it is perhaps along these lines that the greatest advances may yet be made. The dependence of growth and the development of sex characteristics on the anterior lobe is well established, as is also the connection between the posterior lobe and normal metabolism. The early stages of acromegaly and of giantism are definitely associated with a hyperactivity of the gland, while hypopituitarism leads to the syndrome known as *dystrophia adiposogenitalis*. But the picture is extraordinarily complicated. The progress of acromegaly may involve first a hyperplasia and later a destruction of the gland, so that the symptoms of hypersecretion are superseded by quite the opposite ones. A further complication arises in that the symptoms may vary according as the anterior or posterior lobe is mainly involved. Moreover the abnormal functioning of the pituitary is ordinarily associated with a tumor of the gland, so that the symptoms incident to its presence are superimposed upon the pituitary syndrome. Administration of the gland or its preparations has indeed given favorable results in the late stages of acromegaly, as well as in *dystrophia adiposogenitalis*. But it seems certain that along this line the greatest developments must be still to come.

Along another line, however, the pituitary has yielded a product of wide therapeutic interest. If a water extract of the posterior lobe is made, and proteins and other inert material removed, there results a solution of extraordinary physiological activity. It is a powerful stimulant of plain muscle. It affects the blood pressure and heart action. It stimulates the uterus, intestines and bladder, and exercises a definite action on the activity of the kidneys. It is upon these physiological properties that the use of pituitary extract has in the main been based.

Its effect on the heart and the blood vessels renders it valuable in cases of shock and other conditions of low blood pressure. Its use in the shock following operative procedure has been followed by strikingly good results. The improvement in blood pressure and heart action comes into evidence a few minutes after its intramuscular injection. It has the immense advantage that the effect is persistent, lasting as long as from twelve to sixteen hours. Moreover the tendency to reaction when the effect has worn off is but transitory, and the patient has been tided over the most trying period.

Its stimulating action on the uterus was one of the first properties noted, and in obstetrics and gynecology pituitary solution has perhaps found its greatest use. In uterine inertia and in conditions where the rapid termination of labor has become desirable or imperative it has given prompt and effective results. For the control of postpartum hemorrhage it is rapid and certain. It presents over ergot the advantages of stability, of uniformity secured by an adequate physiological assay, and of unquestionable sterility. Like other powerful drugs it is susceptible of abuse, and its use in labor with insufficient indications has been the subject of some criticism. In gynecology it has proved, by virtue of this stimulating action on the uterus muscle, an efficient hemostatic.

The action of pituitary extract on the intestine and bladder muscles seems to increase in proportion as there is atony and paresis present. Consequently its use in the condition of loss of tone and distention which may follow operative procedure has led to extraordinarily good results. Its action under these circumstances has been so prompt and so certain as to appear almost specific.

That pituitary solution exercises an effect on renal function is not to be doubted, and diuresis has been associated both experimentally and in some cases clinically with disturbances of the pituitary. But the evidence to date has curiously enough led to two absolutely opposite theories—one that diabetes insipidus is caused by hyperactivity of the pituitary gland, the other that it results from pituitary insufficiency. However this may be, it is certain that diabetes insipidus reacts readily to the injection of pituitary solution. The output of urine is cut down to an amount approaching normal, and the distressing symptom of thirst altogether relieved. The effect persists for hours, so that two injections a day are ordinarily sufficient. No untoward effects seem to follow its continued use. One can scarcely assume on the basis of this evidence alone that the pituitary gland normally controls renal function, any more than the fact that its extract stimulates the uterus must involve the conclusion that the gland is responsible for normal labor. But the unusual physiological activity of the extract, in these two instances as in others, have made it a therapeutic agent of wide possibilities.

MINNESOTA PHARMACEUTICAL ASSOCIATION.

33D ANNUAL CONVENTION.

BY E. L. NEWCOMB, SECRETARY.

The thirty-third annual convention of the Minnesota Pharmaceutical Association was called to order by President John F. Danek at 10 A.M., Tuesday, February 13. President Danek in a few well-chosen words introduced Governor J. A. A. Burnquist, who gave a stirring patriotic address in welcoming the pharmacists to the capital city.

Mr. Carl W. Brenner, of Stillwater, the newly elected president of the Minnesota Rexall Club, responded to the address of the Governor. Mr. Brenner called particular attention to the efforts which the pharmacists are making to raise the educational standards of pharmacy. He pointed out that the prerequisite legislation which pharmacists were requesting would benefit not only the public but also those who are engaged in the practice of pharmacy. Legislation to prohibit house-to-house distribution of drugs and medicines was approved not only on account of the demoralizing effect of this practice upon the practice of pharmacy, but also because it favors self-medication and the improper use of drugs and medicines by the general public.

Mayor V. R. Irvin on behalf of the citizens of St. Paul extended a cordial welcome to the visiting delegates. The Mayor's address was enlivened by anecdotes and stories which served to impress his hearers with the warmth of his welcome. Max Menzel, of Pipestone, responded to Mayor Irvin, thanking him for his kindly remarks.

RECEPTION OF DELEGATES.

Mr. S. D. Andrews extended greetings from the National Wholesale Druggists' Association and expressed the hope that the convention would be successful in every way. Dean F. J. Wulling, as president of the American Pharmaceutical Association, extended greetings from that organization and expressed the hope that a much larger number of pharmacists would in the very near future affiliate with the American Pharmaceutical Association and derive the benefits therefrom.

Mr. Thomas H. Potts, secretary of the N. A. R. D., extended the fraternal greetings from that association and complimented the association on their having secured so able and capable a speaker as Mr. Eugene Brockmeyer, counsel for the N. A. R. D. At this time Dean Wulling upon the request of the president introduced Professor Henry Kraemer, of Philadelphia, who responded by congratulating the pharmacists of the Northwest upon the progressive stand which they had taken in matters pertaining to pharmacy.

Secretary Newcomb next gave his annual report which, while mainly statistical, dwelt at some length on a number of the activities of the association. Attention was called to the fact that the active membership has increased during recent years to the extent that over sixty per cent. of all the pharmacists of Minnesota now belong to the association. Committee letters sent out from the secretary's office during the last year approximated twenty thousand. In addition to this large amount of committee work, over eleven hundred personal letters were written by the secretary.

A considerable portion of the secretary's report dealt with the conservation of the printed proceedings of the Minnesota and other state associations. The conservation of pharmaceutical journals was also discussed. An exhibit was arranged, consisting of bound volumes of pharmaceutical journals and printed proceedings, all of which are the property of the association and which had been bound at the direction of the executive committee. A total of some four hundred printed annual records were represented by the exhibit. The value of these publications was emphasized, and the report recommended that the association continue to preserve such material. The secretary stated that there were still about five hundred active registered pharmacists in Minnesota who do not belong to the association. A continuation of the membership campaign was urged in order that all active pharmacists might soon be brought into the work of the organization.

Chairman J. P. Jelinek next presented the report of the legislative committee which dealt chiefly with prerequisite and anti-drug peddling legislation. The general subject of legislation to restrict the indiscriminate sale of drugs and medicines was then discussed. The Minnesota prerequisite bill was read at this time and discussed in order that those who were not clear on some of the provisions might be well informed. Those taking part in the discussion were: Fred Klenert, Minneapolis; Secretary Newcomb, A. J. Kline, R. J.

Messing, St. Paul; Professor Henry Kraemer, Philadelphia, and others. The Minnesota Prerequisite Bill, as read, follows:

Minnesota Prerequisite Bill—Senate File No. 378.

A Bill

For an Act, To Amend Section 2330 of the Revised Laws of 1905, As Amended by Chapter 346 Laws 1907, being Section 5032 General Statutes 1913, relating to qualifications entitling Pharmacists to registration.

Be it Enacted by the Legislature of the State of Minnesota:

Section 1. That Section 2330 of the Revised Laws of 1905, As Amended by Chapter 346 Laws 1907, being Section 5032 General Statutes 1913 be amended so as to read as follows:

5032.—To be entitled to examination by the Board as a pharmacist, the applicant shall be at least twenty-one years old, shall have successfully completed the work of two (2) college years, of not less than seven (7) months each, at a college or school of pharmacy which in the judgment of the Board maintains proper standards, as such, and shall have had at least two (2) years of practical experience in drug stores where physicians' prescriptions are usually compounded; provided however, that if the applicant shall have successfully completed a longer course than two (2) college years, of seven (7) months each, in such school or college of pharmacy, an additional year, or more, so successfully completed, shall be equivalent to one (1) year of such practical experience.

Provided that, any person, who is, at the time of the passage of this amendment, actually employed in a drug store, who shall on or before the first of October, 1917, file with the Board a sworn statement of proof of that fact, or who is registered by said Board as an assistant pharmacist shall be exempt from the requirement of attendance at a college or school of pharmacy, but shall be entitled, if of the required age, to examination upon the completion of four (4) years experience, as the same is herein defined, provided further; that, one (1) year of college work, as herein defined shall be equivalent to one (1) year of experience. If upon examination the Board finds him qualified, he shall be entitled to registration as such pharmacist.

Section 2. This Act shall take effect and be in force from and after its passage.

Commercial Section.

The commercial section was called to order by Chairman H. C. Kruckeberg after the meeting had been turned over by President Danek. After suitable introductory remarks, Chairman Kruckeberg presented his annual address in which he reviewed in an illuminating way some of the difficult commercial problems of the pharmacist. The address was discussed by Dean Wulling and others who were present.

"Questionable Methods of Advertising" was the title of an impromptu address by Mr. W. E. Arford. The speaker described in detail illegitimate methods being employed which have resulted in a number of pharmacists losing considerable sums of money.

At this time, President Binz, of the California Pharmaceutical Association, was introduced and extended the privileges of the floor. Mr. Binz spoke at length on the subject of pharmaceutical legislation. He stated that he had become convinced during the past year that prerequisite pharmaceutical legislation was most essential if pharmacists are to secure other measures which are urgently needed. Mr. Binz extended greetings from the California Association and expressed his appreciation for the cordial reception he had received in Minnesota.

National Legislation.

Mr. Charles H. Huhn presented the report of the committee on national legislation. The report included a consideration of the present status of price maintenance, narcotic legislation, anti-coupon legislation, and other measures of direct importance to pharmacists.

Mr. W. S. Parker, secretary of the North Dakota Board, was next introduced, and spoke upon prerequisite and patent medicine legislation. Sunday closing, Mr. Parker stated, was quite generally observed in North Dakota.

Scientific Section.

Following the address by Attorney Brockmeyer, President Danek turned the meeting over to Dean F. J. Wulling as chairman of the scientific section. Dean Wulling introduced Professor Chas. H. Rogers, who has recently been appointed a member of the faculty of the College of Pharmacy of the University of Minnesota. Professor Rogers brought greetings from the West Virginia Pharmaceutical Association and stated that he hoped to do his share of the work of the University in turning out well-trained pharmacists.

The Northwestern Branch of the American Pharmaceutical Association met jointly with the scientific and practical section, and the following program was carried out:

1. A Symposium on the U. S. P.—IX. Opened and closed by Mr. C. H. Bollinger, and on the N. F.—IV, opened and closed by Mr. F. A. Upsher Smith.
2. Prescription Pricing, by Mr. Robert L. Morland.
3. Duty of the Public to the Pharmacist, by R. J. Messing.

4. Prescriptions and Prescription Compounding, by Mr. H. Martin Johnson.
5. Report of the Committee on Adulteration, by Professor Gustav Bachman.
6. Fractional Percolation, by Mr. O. J. Blosmo.
7. (*a*) The 1916 Results of Medicinal Plant Cultivation for Educational Purposes at the College of Pharmacy, University of Minnesota.
   (*b*) A New Source of Supply for Ergot.
   (*c*) Some Notes on Digitalis with Special Reference to *Digitalis lutea.*
   (*d*) The *Journal* and the *Year Book* of the American Pharmaceutical Association, by E. L. Newcomb.
8. Report of Committee on College of Pharmacy, by Chairman A. J. Kline.

In addition to the above, a paper on "The Prescription Counter," by Mr. R. Bartelson, was read at the Thursday morning session, at which time the usual historical paper by Dean Wulling, of the College of Pharmacy, University of Minnesota, was also presented.

The report of the committee on adulteration by Professor Gustav Bachman elicited favorable comment. The report showed that the general quality of the drugs and medicines reported upon was somewhat higher than the reports heretofore indicated.

The paper on "A New Source of Supply for Ergot," by Secretary Newcomb, was accompanied by an exhibit consisting of different samples of waste cereals containing from seventeen to eighteen per cent. of select ergot. This ergot, the speaker stated, was the equal in pharmaceutical quality to that which is imported from Spain and Russia. It has not come into general use on account of the difficulty in mechanically separating it from the cereal. Mechanical processes have been used so as to concentrate the mixture to nearly fifty per cent. ergot strength.

New Officers for 1917–18.

The following officers, having been duly nominated, were elected to serve the association for the coming year: Louis J. Aberwald, president; Charles MacGregor, Detroit, vice-president; Edward A. Grochau, Duluth, second vice-president; W. C. Haney, Marshall, third vice-president; E. L. Newcomb, secretary; R. J. Messing, treasurer; J. F. Danek, member of the executive committee.

The following were duly nominated as candidates for appointment to the Minnesota State Board of Pharmacy: Max Menzel, Pipestone; Arthur von Rohr, Winona; R. J. Messing, St. Paul; M. G. Johnson, Fulda; and R. E. Desmond, Minneapolis.

Report of Committee on Resolutions.

To the Officers and Members of the Minnesota State Pharmaceutical Association, your committee begs leave to report as follows:

The committee on resolutions has carefully gone over the President's address and approves the following resolutions:

1. That publicity work be continued for the ensuing year on the same plan as during the past year.
2. That the work of the Legislative Committee be commended and approved.
3. In view of the anti-drug-vending measure now being formulated by our Legislative Committee, your Resolutions Committee recommends that no action be taken at this time on recommendation No. 3 (of the President).
4. That we reaffirm a strong conviction in the justice of price maintenance and pledge ourselves to aid any effort of legislation in that direction.
5. That we urge closer coöperation between pharmacists and physicians.
6. That we continue our affiliation with the N. A. R. D.
7. We recommend that a scholarship be established to provide for the tuition for one year for one student at the College of Pharmacy of the University of Minnesota, same to be accredited to the student completing the second year with the highest rating, and being a citizen of the United States and a resident of the State at least five years.
8. That our association again voice its strong disapproval of the use of trading stamps and coupons, in merchandising.
9. We recommend that early closing be dealt with by individual communities.

Your committee recommends that publicity work be continued, as outlined in the report of the committee.

We recommend that the report of the Legislative Committee be adopted as presented and urge all members to coöperate in support of the bills now pending in the Legislature.

After careful consideration of the secretary's report, we recommend that same be adopted, and we further recommend that a hearty vote of thanks be extended to those who have contributed to the completion of the files of pharmaceutical proceedings in the various states. We also recommend that the association extend a rising vote of thanks to our secretary for his untiring efforts in establishing a complete set of proceedings and recommend the continuance of same.

We further recommend that the secretary prepare a yearly inventory of the visible assets of the association to be incorporated in his annual report.

We commend the efficient manner in which the financial and business affairs of the association have been conducted during the past year.

Considering the recommendation of scholarship, your committee feels that the matter is well covered for the present, by the recommendation as noted above.

We recommend that the purchase and selection of a permanent badge or button be left to the discretion of the executive committee.

Your committee commends the efficient and statistical report of the committee on dispensing by physicians.

It being clearly shown that the logical solution of the evil lies with the druggist in his respective locality, we recommend that the druggists be urged to supply physicians in their respective localities with the N. A. R. D. therapeutic topics.

Your committee on resolutions recommend that the work of the Publicity Committee be continued along the lines followed during the past year; that an appropriation of $300 again be made for stenographic assistance; that the committee make an effort to issue one bulletin per month during the coming year; that the pharmaceutical journals be thanked for their coöperation.

We recommend that Professor Henry Kraemer, of Philadelphia, be elected an honorary member of this association.

We urge a rising vote of thanks to be extended to Mr. Eugene Brockmeyer, Professor Henry Kraemer and Thos. H. Potts for their presence, their interesting and valuable addresses and the commendable efforts which they have made for pharmacy.

Your committee further recommends a hearty vote of thanks to W. E. Burke for his untiring efforts in promoting the success of this meeting.

Your committee desires to express its appreciation of and thanks for the help in contributing toward the success of this meeting, by the Travelers' Auxiliary, the Northwestern Druggist, the faculty of the State University, the officers and members of the various committees and to Mr. Haueter for his splendid work in securing new members.

The committee also desires to express its appreciation to Dr. Newcomb for his services during the past year.

We wish to thank the press and the managers of the Saint Paul Hotel for the splendid accommodations and service rendered the association during the meeting.

Respectfully submitted,

Committee: J. P. JELINEK, R. J. MESSING, W. A. ABBETT, MAX MENZEL, HENRY RAUCH.

Owing to the short amount of time available to your committee, we recommend that the secretary prepare suitable memorials expressing the sympathy of the association on the demise of the following: A. D. THOMPSON, WM. MELENDY, H. H. MEYER, MARTIN I. WILBERT, DR. E. K. OGDEN, DR. W. G. BREDE and EDWIN F. WARREN.

The report of the Resolutions Committee was adopted in its entirety.

Chairman Jelinek of the Legislative Committee presented at this time the preliminary draft of the anti-drug-vending bill. The bill provides for the absolute prohibition of the sale of drugs and medicines by the itinerant vendor. After some discussion the measure was tentatively adopted and referred to the Legislative Committee for re-drafting and introduction.

SCIENTIFIC SECTION (*continued*).

President Danek requested Dean Wulling to preside during the completion of the scientific section program. Dean Wulling introduced Professor Henry Kraemer, of the Philadelphia College of Pharmacy, who delivered an illustrated lecture on "Pharmacognosy in its Relation to the Practice of Pharmacy." Professor Kraemer gave his personal views as to the subject matter of practical pharmacognosy in its relation to the retail druggist. He dwelt upon its relation to the study of the raw materials and products manufactured from them. He pointed out clearly the difference between pharmacognosy and materia medica, both in the subjective

treatment and the objects to be attained in the respective sciences. Emphasis was laid upon the fact that pharmacognosy is an active discipline and is concerned with the solution of every-day problems and the producing of tangible results. In the subsequent illustrated lecture many opportunities were indicated to show how the retail pharmacist could apply his professional knowledge and thereby make himself more valuable to the public and to himself. Professor Kraemer said: With Josh Billings we say, "It is better to know a few things right than many things that are not so." In the teaching of pharmacognosy he said: "I continually say to my classes that they only know what they can do. As a student, you may state a fact, but it is yours only when you can demonstrate it." The essential practicability of the science of pharmacognosy was emphasized, and in that connection it was pointed out how essential the science is to the pharmacist, because he deals with so many crude drugs and other raw materials, and hence is vitally concerned with their identity and quality. Professor Kraemer's wonderful collection of slides was divided into two classes: (1) Those dealing with the identification and determination of the quality of commercial drugs and allied products; (2) those dealing with the determination of the composition of complex commercial products. In connection with the latter, many valuable suggestions were given as to the opportunity of the pharmacist in the manufacturing line. The lecturer showed a series of about 150 magnificent lantern slides, many of them having been colored by Professor Kraemer himself.

OBITUARY.

William C. Alpers, dean and professor of pharmacy at the School of Pharmacy of Western Reserve University, Cleveland, Ohio, died on February 22, 1917. Professor Alpers was born at Hanover, Germany, July 7th, 1851. After the close of the Franco-German war, in which he took part, he came to America. Later he attended the New York College of Pharmacy and the University of New York, receiving the degree of doctor of science in chemistry from the latter institution. Dr. Alpers was always prominent in organized pharmacy, being at one time the president of both the New Jersey and the American Pharmaceutical Associations. Dr. Alpers's funeral took place in New York and was largely attended.